Cardiovascular disease continuum after preeclampsia

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ENGLISH SUMMARY

Cardiovascular disease is the main cause of death in women worldwide, and the second cause of death in The Netherlands. It has become evident that women who have had preeclampsia, a hypertensive pregnancy disorder, face an increased cardiovascular risk later in life.

The Dutch guideline 'Cardiovascular risk management after reproductive and pregnancy-related disorders' recommends that women with a history of preeclampsia should undergo a cardiovascular risk assessment at the age of 50. Choosing the age of 50 was a pragmatic choice rather than scientifically founded, since the course of cardiovascular risk factors over time among these women is largely unknown. Therefore, this thesis focuses on women's cardiovascular risk profile in the fifth decade of life, between their 40's and 50's, in relation to a history of early-onset preeclampsia.

This thesis is divided in four parts. The first part gives an introduction of the hypertensive pregnancy disorder preeclampsia, cardiovascular disease in women and the increased risk of cardiovascular disease after preeclampsia. The second part focusses on the assessment of cardiovascular risk factors, established CVD and diastolic dysfunction in women with history of early-onset preeclampsia. Research was conducted in the fifth decade of life, when premature cardiovascular diseases are expected to develop. The third part consists three studies on cardiovascular risk perception in women with a history of preeclampsia. The fourth part includes the general discussion and summary of the thesis.

Part I – Introduction

Chapter 1 provides a general introduction and reveals gaps in the research of women in the fifth decade of life, with a history of early-onset preeclampsia, and the corresponding objectives achieved in this thesis.

Chapter 2 further introduces the comprehensive disease of preeclampsia. Preeclampsia is a common pregnancy specific disease with major impact in long term outcome for both women and their children. This review gives the most recent insight with focus on impact on the fetus, short and long-term outcome of offspring's, and long-term outcome of women with a history of preeclampsia. Women with a history of preeclampsia are prone to cardiovascular disease later in life. This implies the opportunity to develop and evaluate preventive programs at a relative young age. In addition, the effects of maternal treatment, the medication she receives, and the exposure to a deprived intrauterine environment, on long-term outcome for children is unclear and should therefore be examined.

Part II – Cardiovascular risk factors after preeclampsia

Chapter 3 presents a prospective observational study in which we assessed cardiovascular risk factors and established cardiovascular disease in women after early-onset preeclampsia, in the fifth decade of life. Early-onset preeclampsia was diagnosed as delivery before 34 weeks' gestation, blood pressure >140/90 mmHg, and proteinuria >300 mg/24 h. 131 women with a history of early-onset preeclampsia were compared to 56 women with a history of uncomplicated pregnancy, 9-16 years after their index pregnancy. Cardiovascular risk assessment consisted of a questionnaire, blood pressure measurement, anthropometrics, and laboratory screening of blood and urine. Women with a history of early-onset preeclampsia had significantly greater systolic and diastolic blood pressure, greater body mass index, more often an abnormal lipid profile (lower high-density lipoprotein levels, higher triglycerides), greater glycated hemoglobin, and greater levels of albuminuria compared to controls. None of the women with a history of early-onset preeclampsia was diagnosed with cardiovascular disease; 38.2% was diagnosed with hypertension; and 18.2% was diagnosed with metabolic syndrome. In women with a history of an uncomplicated pregnancy, no women were diagnosed with cardiovascular disease; 14.3% were diagnosed with hypertension; 1.8% with metabolic syndrome. We have showed that women with a history of early-onset preeclampsia had major cardiovascular risk factors, compared to women with an uncomplicated pregnancy in history, RR 2.7 for hypertension and RR of 9.0 for metabolic syndrome. These women are currently outside the scope of most preventive programs due to their relatively young age, but have important modifiable risk factors for cardiovascular diseases.

Chapter 4 describes a systematic review and meta-analyses on shared biomarkers between preeclampsia and heart failure with preserved ejection fraction (HFpEF). These shared markers represent common pathogenic pathways between both diseases and might be potentially eligible for cardiovascular risk stratification in women after hypertensive pregnancy disorders. A first literature search was conducted to assess blood markers in women with diastolic dysfunction. With a second literature search we investigated whether these same biochemical markers were present in preeclampsia. The first search on biomarkers discriminating women with HFpEF from female controls, yielded 13 studies on 11 biochemical markers. The second search was for studies discriminating women with pre-eclampsia from women with non-hypertensive pregnancies with at least one of the biomarkers found in the first search. After the second search 51 studies on seven biomarkers were included in meta-analyses and 79 studies on 12 biomarkers in systematic review. Eleven biological markers differentiated women with diastolic dysfunction from controls, of which the following 10 markers differentiated women with pre-eclampsia from controls as well: C-reactive protein, HDL, insulin, fatty acid-binding protein 4, brain natriuretic peptide, N terminal pro brain natriuretic peptide, adrenomedullin, mid-region pro adrenomedullin, cardiac troponin I, and cancer antigen 125. Our study supports the hypothesis that HFpEF in women shares a common pathogenic background with preeclampsia. The biomarkers representing inflammatory state, disturbances in myocardial function/structure, and unfavorable lipid metabolism may possibly be eligible for future prognostic tools.

Chapter 5 presents the parameters regarding heart failure with preserved ejection fraction (HFpEF) in all women who participated in the cardiovascular risk assessment study described in chapter 3. Early-onset preeclampsia and HFpEF share common mechanistic hallmarks including systemic inflammation, endothelial dysfunction and deficient vascularization of either uterus or myocardium. HFpEF is preceded in middle age by preclinical left ventricular diastolic dysfunction. 131 women with a history of early-onset preeclampsia were compared to 56 women with a history of uncomplicated pregnancy to assess echocardiographic indices of ventricular function and structure and biomarkers of systemic inflammation or endothelial dysfunction. Women with a history of preeclampsia had higher body mass index, blood pressure and plasma levels of interleukin-6 and soluble intercellular adhesion molecule-1 (sICAM-1). They had thicker septal and posterior left ventricular walls and worse diastolic left ventricular function evident from reduced mean mitral annular lengthening velocity (E'mean) and higher ratio of early diastolic mitral flow velocity (E) over E'mean (E/E'mean). Differences of sICAM-1, E'mean and E/E'mean remained significant after accounting for BMI and blood pressure. This study showed that a history of preeclampsia predisposes in middle age to worse left ventricular diastolic

function, which could increase the likelihood of later HFpEF development. This predisposition derives not only from persistent cardiovascular risk but probably also from persistent endothelial dysfunction hindering adequate vascularization in the uterus during pregnancy and in the myocardium in middle age.

Part III – Cardiovascular risk perception after preeclampsia

Chapter 6 describes the ability of women to recall hypertensive disorders in pregnancy in their fifth decade of life and whether they can differentiate between early-onset, late-onset preeclampsia and gestational hypertension. Women with history of early-onset preeclampsia, late-onset preeclampsia, gestational hypertension, uncomplicated pregnancy or preterm birth were asked to participate 5 to 10 years after their index pregnancy. Maternal recall was assessed using a questionnaire and compared to medical records. We found that the recall of early-onset preeclampsia had a sensitivity of 98.1% and specificity of 94.2%, recall of late-onset preeclampsia had a lower sensitivity of 68.2% and specificity of 91.1% and gestational hypertension had only a sensitivity of 29.0% and specificity of 97.9%. Furthermore we found that lower gestational age at delivery was associated with higher rates of correct maternal recall (OR 0.734, 95% CI: 0.658-0.819). So, the shorter the gestational age, the better the recall. These results demonstrate that early-onset preeclampsia can accurately be assessed using a simple questionnaire. Recall of late-onset preeclampsia and gestational hypertension was less accurate. These last mentioned women overstated their risk by recalling a more severe hypertensive disorder. In clinical practice this would be suitable to detect most women at risk.

Chapter 7 evaluates the effect of communicating cardiovascular risk factors on intended healthy behavior in women with a history of preeclampsia or uncomplicated pregnancy. It is often assumed that it is motivating for an individual to be informed about the presence of risk factors, but studies supporting this assumption were lacking. The intention for healthy behavior, as a proxy for actual behavior, was assessed before and after a cardiovascular risk assessment. Healthy behavior was subdivided in healthy diet, sufficient exercise and smoking cessation for smoking participants. Following the risk assessment, two groups were distinguished: women who did not have cardiovascular risk factors at risk assessment and those who had one or more risk factors. In women with cardiovascular risk factors, the intention to quit smoking increased, whereas intended healthy diet and sufficient exercise did not change. In participants without risk factors, none of the healthy behaviors changed. This study showed that communicating risk factors in women who face an increased cardiovascular risk after preeclampsia does not seem to be effective as a stand-alone intervention.

Chapter 8 analyses the effect of framing, the perceived probability and its interaction, on the willingness to modify behavior to reduce cardiovascular risk after preeclampsia. In promoting healthy lifestyle, it has been demonstrated that even subtle differences in message framing can affect health-related behavior. Cardiovascular risk for example can be presented in health score as 'chance to stay healthy' or risk score as 'risk to develop a disease'. Another important factor influencing people's motivation is the perceived probability of developing a disease. When confronted with a perceived high risk, people are more willing to modify their behavior than when the risk is perceived as low. We have studied this in 165 O&G nurses who had to fill in a questionnaire with two hypothetical scenarios, a case with mild preeclampsia and a case with severe preeclampsia. Case information was given in health score or risk score. After each scenario they had to score the willingness to modify their behavior. We found a significant main effect of the severity of the case, a non-significant main effect of framing and a non-significant interaction between severity and framing on the willingness to modify behavior. Framing information in health score or risk score and its interaction with probability was not of influence in motivating patients to modify their lifestyle to decrease cardiovascular risk after preeclampsia. Framing in health or risk score, therefore, did not seem to be contributing in clinical practice.

Part IV – Discussion

Chapter 9 provides a general discussion of this thesis. The findings are discussed in light of four questions, each ending with a conclusion and suggestions for future research.
Women with a history of early-onset preeclampsia have major cardiovascular risk factors and high prevalence of preclinical diastolic dysfunction already in the fifth decade of life, with a mean age of 44 years. Currently, this group of women does not receive attuned health care.